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Association between abdominal aortic calcification, bone mineral density and fracture in older women

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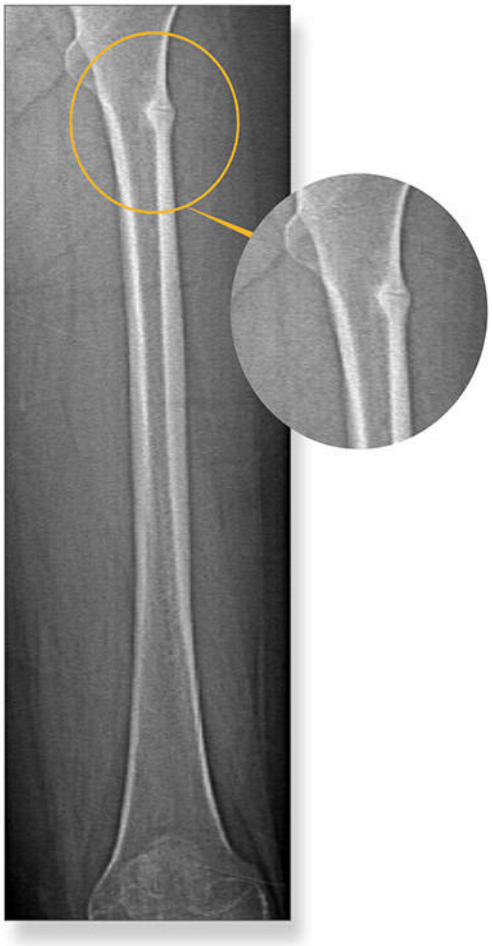

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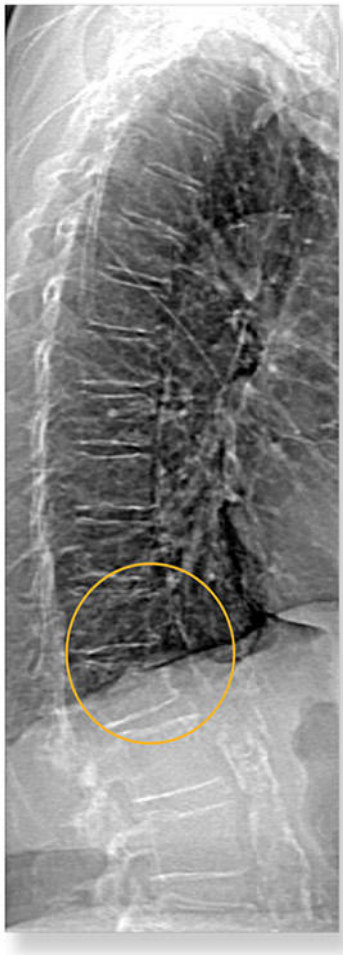

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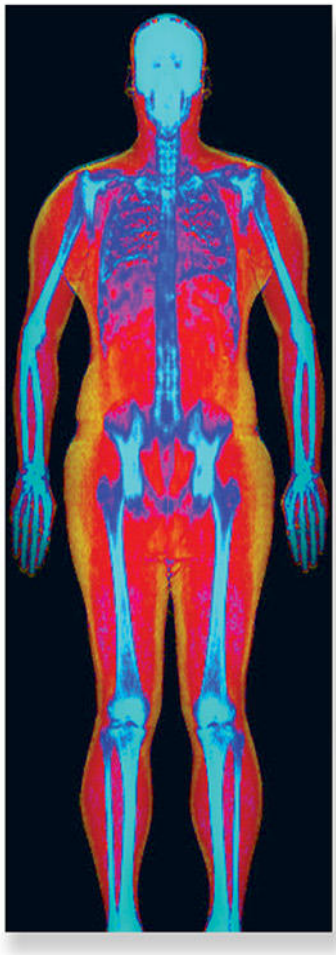

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DISCLOSURES

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ABSTRACT

Although a relationship between vascular disease and osteoporosis has been recognized, its clinical importance for fracture risk evaluation remains uncertain. Abdominal aortic calcification (AAC), a recognized measure of vascular disease detected on single-energy images performed for vertebral fracture assessment, may also identify increased osteoporosis risk. In a prospective 10-year study of 1,024 older predominantly Caucasian women (mean age 75.0±2.6 years) from the Perth Longitudinal Study of Aging cohort we evaluated the association between AAC, skeletal structure and fractures. AAC and spine fracture were assessed at the time of hip densitometry and heel quantitative ultrasound. AAC was scored 0 to 24 (AAC24) and categorized into; low AAC (score 0 and 1, n=459), moderate AAC (score 2-5, n=373) and severe AAC (score $\geq$ 6, n=192). Prevalent vertebral fractures were calculated using the Genant semi-quantitative method. AAC24 scores were inversely related to hip bone mineral density (BMD) (r_s=-0.077, p=0.013) and heel broadband

ultrasound attenuation (r_s=-0.074, p=0.020) and stiffness index (r_s=-0.073, p=0.022). In cross-sectional analyses women with moderate to severe AAC were more likely to have prevalent fracture and LSI detected lumbar spine but not thoracic spine fractures (Mantel-Haentzel test of trend $p < 0.05$). For 10-year incident clinical fractures and fracture-related hospitalizations women with moderate to severe AAC (AAC24 score >1) had increased fracture risk (HR 1.48 [1.15-1.91], p=0.002; HR 1.46 [1.07-1.99], p=0.019, respectively) compared to women with low AAC. This relationship remained significant after adjusting for age and hip BMD for clinical fractures (HR 1.40 [1.08-1.81], p=0.010) but was attenuated for fracture-related hospitalizations (HR 1.33 [0.98-1.83], p=0.073). In conclusion, older women with more marked AAC are at higher risk of fracture, not completely captured by bone structural predictors. These findings further support the concept that vascular calcification and bone pathology may share similar mechanisms of causation that remain to be fully elucidated.

KEY WORDS: Vascular calcification, Abdominal aortic calcification, Bone mineral density**,** heel quantitative ultrasound, Fractures.

INTRODUCTION

Vascular and bone diseases are considered to share common pathophysiological mechanisms. In particular arterial calcification processes have been shown to share some pathways in common with bone physiology.(1) At the clinical level osteoporosis and low bone mineral density (BMD) have been linked to a small increase in cardiovascular disease (CVD) risk in older populations potentially related to vascular calcification.(2) AAC is a marker of advanced atherosclerosis in other vascular beds including the thoracic aorta and iliac arteries,(3) carotid arteries

(4) and coronary arteries.(3,5) We and others have identified abdominal aortic calcification (AAC) as a marker of atherosclerotic vascular disease that may be involved in the association of bone and vascular disease.(6)

It is important to understand that calcification of arterial tissue is not merely a passive process of calcium phosphate precipitation, but a highly organized process, regulated by mechanisms similar to those involved in bone mineralization.(7,8) Atherosclerotic lesions tend to originate around the major vessel bifurcations and the branching arteries. Branching arteries in the abdominal aorta supply blood and nutrients to the lumbar vertebrae. Therefore, occlusion of these arteries may result in ischemia in the lumbar spine, which can lead to degeneration and asymptomatic vertebral fractures.(9) Furthermore, local and systemic osteochondrogenic factors can be released by calcified atherosclerotic lesions, which can affect regional and systemic bone homeostasis. (10,11)

In this paper we explore the hypothesis that the presence and severity of AAC is related to bone structure, prevalent fractures and incident fractures using the same population in which we previously identified an association between AAC and CVD.(6) To do this we used lateral spine imaging undertaken at the time of bone density testing.(12)

METHODS

This article complies with the STROBE reporting guidelines for observational studies.

Study Population

In 1998, older women were recruited to a 5-year prospective, randomised, controlled trial of oral calcium supplements to prevent osteoporotic fractures, the Calcium Intake Fracture Outcome study (CAIFOS). This study continued as an epidemiological study, the Perth Longitudinal Study of Aging Women (PLSAW).(13) The trial was retrospectively registered in the Australian New Zealand Clinical Trials Registry (ACTRN12615000750583) as it was commenced and completed before the advent of the clinical trials registry. Participants were recruited from the Western Australian general population of women aged over 70 years by mail using the electoral roll, which is a requirement of citizenship. Of the 5,586 women approached, 1,500 women were recruited into the study. All participants were ambulant with an expected survival beyond 5 years and were not receiving any medication (including hormone replacement therapy) known to affect bone metabolism. Baseline disease burden and medications were comparable between these participants and the general population of similar age.(13) In the subsequent 5 years following inclusion in the study, participants received 1.2 g of elemental calcium as calcium carbonate daily or a matching placebo. For the present study, women were included in the analysis if lateral spine images (collected in 1998 or 1999) and measurements of hip BMD were both available (n=1,024). The Human Ethics Committee of the University of Western Australia approved the study and written informed consents were obtained from all participants. Human ethics approval for the use of linked data for the project was provided by the Human Research Ethics Committee of the Western Australian Department of Health (DOHWA HREC), project number #2009/24.

Baseline risk assessment

Participants provided their medical history and current medications verified by their General Practitioner. These data were coded using the International Classification of Primary Care – Plus (ICPC-Plus) method.(14) The coding methodology allows aggregation of different terms for similar pathologic entities as defined by the ICD-10 coding system. These data were then used to determine the presence of pre-existing diabetes (T89001-90009). Cardiovascular medications included anti-hypertensive medications, statins and low dose aspirin. Smoking status was coded as non-smoker or ex-smoker/current smoker if they had consumed more than 1 cigarette per day for more than 3 months at any time in their life. Weight was assessed using digital scales with participants wearing light clothes and no shoes. Height was assessed using a stadiometer and the body mass index was calculated in kg/m^2 at baseline. Self-reported prevalent fractures were recorded if the fractures (i) occurred after the age of 50 years, (ii) were due to minimal trauma defined as falling from standing height or less, and (iii) not a fracture of the face, skull, or phalanges.

Bone measurements

Total hip bone mineral content (BMC) and density (BMD) was measured by Dual Energy X-ray Absorptiometry (DXA) using the Hologic Acclaim 4500A fan beam densitometer (Hologic Corp, Waltham, MA, USA) at baseline (1998) or year one (1999). The coefficients of variation (CV) at the total hip was 1.2% in our laboratory.(15) Quantitative heel ultrasound (QUS) of the calcaneus of the left foot was measured in duplicate using a Lunar Achilles Ultrasound machine (Lunar Corp., Madison, WI, USA) at baseline in 990 women. The average measurement of the

Speed of Sound (SOS), Broadband Ultrasound Attenuation (BUA) and Stiffness index (SI) were determined. The CV were 0.4% for SOS and 1.6% for BUA.

Lateral spine imaging

Digitally enhanced lateral single-energy images of the thoraco-lumbar spine were collected using the same Hologic 4500A machine (Hologic, Marlborough, MA, USA). A single experienced investigator (JTS), read all images and scored vertebral fractures using the Genant semi-quantitative method.(16) We included the modification that grade 1 fractures were considered fractures only if there was clear endplate depression or cortical discontinuity, as described in a prior publication.(17) The same investigator calculated all AAC scores from 0 to 24 using the established technique.(18-20) This investigator was blinded to all study participant characteristics and outcomes. Severity of AAC was categorized using previously published groupings for cardiovascular disease: low (AAC24 score 0 or 1), moderate (AAC24 score 2-5) and severe (AAC24 score 6 or greater) AAC scores.(20)

Biochemistry

Fasting blood samples were collected at baseline (1998). Total cholesterol, high-density lipoprotein cholesterol (HDLC), serum calcium, serum phosphate and creatinine were measured. Creatinine was used to estimated glomerular filtration rate (eGFR). A detailed description of the methods related to the measurement of all circulating biological markers can be found in **Supplementary Text 1**.

Clinical fractures & fracture hospitalizations

The primary outcomes were incident clinical fracture and fracture hospitalizations. Incident clinical fractures were captured using an adverse events

diary collected every 4 months during the first 5 years and every 6 months during the subsequent 5 years of follow up (total of 10 years). From these self-reported fractures, low trauma clinical fractures resulting from falling from standing height or less, including minimally traumatic symptomatic vertebral fracture, were recorded (clinical fractures). All fractures were confirmed by radiographic records or General Practitioner reports. Hip and fracture-related hospitalizations over 10 years (1998-2008) were identified using the Hospital Morbidity Dataset Collection, linked via the Western Australian Data Linkage System (WADLS). This system allows identification of admission to and discharge from all hospitals in Western Australia. Diagnosis codes were defined using the *International Classification of Diseases, Injuries and Causes of Death: Clinical Modification* (ICD-9-CM) codes 1998-1999 (21) mapped to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10- AM) for 1999-2013. (22) Codes used for identification were S02.0-S02.9, S12.0-S12.9, S22.0-S22.9, S32.0-S32.9, S42.0-S42.9, S52.0-S52.9, S62.0-S62.9, S72.0-S72.9, S82.0-S82.9, S92.0-S92.9, M80, T02, T08, T10, T12 and T14.2. Fractures of the face (S02.2-S02.6), fingers (S62.5-S62.7), and toes (S92.4-S92.5) and fractures caused by motor vehicle injuries (External cause of injury codes V00-V99) were excluded.

Estimated fracture risk

The FRAX Australian major osteoporotic fracture risk prediction was determined using the calculator on the FRAX website (www.shef.ac.uk/FRAX). Baseline data were used to calculate the estimated 10-year risk of fracture using the FRAX Australian with and without BMD. Data used including: age, sex, weight (kg), height (cm), previous fracture, parental history of hip fracture, current smoking,

glucocorticoid use, history of rheumatoid arthritis or secondary osteoporosis and intake of 3 servings of alcohol per day. Data were input with and without femoral neck BMD (g/cm^2). Secondary osteoporosis was an exclusion criteria for the initial randomized controlled trial and data on parental hip fracture was unavailable and was left blank meaning the answer to this question was assumed to be "no" for all women.

Statistical analysis

Baseline data are presented as either mean ± SD, median and IQR or number and (%) where appropriate. Chi squared tests or ANOVA to test the difference between severity of AAC (low AAC24 scores 0 or 1, moderate AAC24 scores 2-5 and severe AAC24 score ≥6) was applied where appropriate. Spearman's rank correlation and age and treatment-adjusted partial correlation statistics were calculated for the correlation between AAC24 and hip BMD and heel ultrasound measures. Generalized additive model (GAM) was undertaken using the R package "mgcv"(23) to generate GAM graphic representations of the dose-response relations between AAC24 and the bone structural variables BMD and heel BUA, adjusted for age and treatment group, with method = REML and knots = NULL. Logistic regression was used to examine the relationship between AAC and prevalent fractures in unadjusted and age, treatment and total hip BMD-adjusted models. The primary outcomes were the hazard ratio (HR) for any incident clinical fracture or fracture hospitalization up until 10 years. We performed analysis using three models: (Model 1) AAC unadjusted, (Model 2) model 1 + age and treatment (placebo vs. calcium or calcium with vitamin D2) adjusted and (Model 3) model 2 + total hip BMD adjusted analyses. For the primary Cox regression analyses, we treated deaths as censored. This approach means that the HRs can be interpreted as the risk of fracture for any time during follow-up

assuming that a woman stayed alive for that long. No violations of the Cox proportional hazards assumptions were detected. To investigate the non-linear relationship between AAC24 and incident fracture outcomes, hazard ratios (HRs) with 95% confidence intervals (CIs) were derived from Cox proportional hazard regression for each AAC24 point increase using AAC24=2 as the reference and 3 knots. To investigate whether the association between AAC and incident fractures was modified by fracture risk factors or biomarkers we undertook interaction testing in age and treatment–adjusted models, with P<0.1 considered significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA) and Stata software, version 14 (StataCorp LLC, College Station, Texas, USA). Statistical significance was set at a two-sided Type One error rate of $p< 0.05$ for all tests.

RESULTS

The participants mean (SD) age was 75.0 (2.6) years (n=1,024), with AAC present (AAC24 score > 0) in 72.9% of women. The median AAC score was 2 with an IQR of 0 and 4 (range = 0 to 18). Baseline characteristics of participants in the three AAC severity groups are presented in **Table 1**. Age was marginally higher in the moderate and severe AAC groups. Both of these groups had an increased proportion of previous or current smokers compare to the low AAC group but not prevalent diabetes

AAC and cross-sectional measures of bone structure

AAC24 scores and bone structure were inversely related before (hip BMD Spearman's rank rho=-0.077, p=0.013), heel BUA (rho=-0.074, p=0.020) and

stiffness index (rho=-0.073, p=0.022) and after adjusting for age and treatment code (hip BMD r=-0.075, p=0.017, heel BUA r=-0.080, p=0.012 and stiffness index r=-0.072, p=0.024). Women with severe AAC had a lower total hip BMD, heel BUA and stiffness index than those with low AAC in unadjusted analyses, with hip BMD and heel BUA remaining significant even after adjusting for age and treatment (**Supplementary Figure 1**). To investigate the "dose-response" relationship between AAC24 point scores and these bone measures further, we used age and treatment-adjusted generalized additive model (**Supplementary Figure 1**).

AAC and cross-sectional relationship with prevalent fractures (Table 1)

Women with more severe AAC were more likely to have sustained one or more osteoporotic fractures since the age of 50 compared to those with low AAC in unadjusted analyses (OR 1.53 [1.05-2.24], p=0.026). However adjusting for age, treatment and total hip BMD, attenuated this relationship (OR 1.45 [1.00-2.11], p=0.051). Women with severe AAC were more likely to have a lumbar spine vertebral fractures seen on the lateral spine image in unadjusted (OR 1.74 [1.02-2.95, p=0.042, p=0.048). However, adjusting for age, treatment and total hip BMD, attenuated these relationships (OR 1.61 [0.94-2.74, p=0.084).

AAC and 10-year incident fractures

Over 8,135 person years of follow up, 253/1,024 (24.7%) women had experienced a clinical fracture while 169/1,024 (16.5%) were hospitalized for fractures (9,122 person years of follow-up). The Kaplan Meier curves for time to first clinically reported fracture or fracture-related hospitalization are shown in **Figure 1**. These data identified that the fracture risk was similar in participants with moderate

and severe AAC, thus these categories were combined for all subsequent analyses (**Table 2**). Compared to women with low AAC, women with moderate to severe AAC had increased risk of all clinical and clinical spine fractures and all hospitalized fractures, but not hip fractures. However, after further adjustment for total hip BMD, only clinical fracture, which included vertebral fractures remained significant (**Table 2**). To explore the non-linear relationship between AAC24 and fracture, age and treatment restricted cubic splines were constructed (**Supplementary Figure 2**). A competing risk analysis including mortality as the competing risk obtained comparable results (**Supplementary Table 1**). Interaction testing identified a significant interaction (p=0.033) between AAC24 scores and prevalent VF, whereby the association of both moderate to severe AAC and prevalent vertebral fracture with incident clinical fracture was stronger in the presence of the other (**Figure 2**). However no interactions were observed for fracture hospitalizations or self-reported fractures since the age of 50 years.

Potential clinical risk factors for incident fracture risk

To assess the robustness of the findings, further analyses were performed adjusting for estimated fracture risk (FRAX) with and without BMD **Supplementary Table 2**. We also undertook extensive testing of individual clinical effect modifiers to identify whether the association between AAC and incident fractures were different in women with different clinical fracture and cardiovascular risk factors (**Table 3**). This analysis identified HDLC as a potential effect modifier whereby the strongest association between AAC and fractures was seen in people with higher levels of HDL cholesterol. We did not identify any other clinical risk factors modifying the relationship between AAC and fracture risk.

DISCUSSION

We confirmed previous associations between increased severity of AAC with low total hip BMD, and increased prevalent fractures and LSI detected lumbar vertebral fractures. We also demonstrated that AAC was related to heel quantitative ultrasound measures of bone quality. Furthermore for prospective fracture outcomes, both moderate to severe AAC was associated with increased risk of clinical and serious fractures requiring hospitalization. Importantly, we observed similar associations with both self-reported verified clinical fractures as well as fracture hospitalisations that are independent of self-report increasing the confidence in the findings. The associations also remained similar when undertaking competing risk analysis, suggesting survival bias does not explain the relationship between AAC and fracture.

The findings that severe AAC are associated with lower hip bone mineral density are in accord with those of Bagger et. al. (24), who found in a large cohort of postmenopausal women (n=2,662, mean age= 65 years) that women with AAC24 scores ≥3 had lower hip and spine BMD, independent of age and BMI. Similarly, Szulc et al found in a cohort of men (n=781, age≥ 50 years) that individuals with severe AAC (AAC24 scores >6) had significantly lower BMD at a number of sites than those with AAC24 scores ≤6 over 10 years. (25) However, two cross-sectional studies of older women reported that the association between AAC and BMD were non-significant after adjusting for age.(26,27) However these studies only assessed the association between the presence of any AAC and BMD, without accounting for the severity. Additionally, our study also investigated and demonstrated severe AAC was associated with lower heel BUA. Collectively, the present literature suggests that

more advanced AAC is associated with lower BMD of the skeleton at multiple sites by an as yet unknown mechanism.

Regarding mechanism(s) in this study, a possible explanation is that AAC impairs vascular supply of oxygenated blood and nutrients to the skeleton at both the hip and heel bone. Additionally, as the abdominal aorta supplies oxygenated blood to the intestines via the mesenteric arteries, reduced vascular supply may also lead to malabsorption of essential nutrients and vitamins. Another potential mechanism is circulating factors from the "injured" calcified vasculature affecting BMD at multiple skeletal sites such as the observed relationship to the hip and heel bones. Alternatively, there are well known shared genetic and environmental risk factors for both the skeleton and the vasculature.(28)

Regarding the association of baseline AAC and with self-reported fractures from the age of 50 years and the number and severity of prevalent vertebral fractures of the lumbar spine. The data confirm and expand upon previous cross-sectional studies investigating the association between AAC and prevalent fracture, including the cross-sectional study of older men and women by Naves et al. (29) and the cross-sectional study of the STRAMBO cohort of older men by Szulc et al. with prevalent vertebral fractures.(30)

To our knowledge this is the first study to have investigated the association of severe AAC reporting the vertebral fractures of the thoracic and lumbar regions separately. The association between AAC and incident fractures was most pronounced for clinical spine fracture that are often associated with substantial pain, morbidity, and loss of mobility that is comparable to hip fractures.(31-34) Given that the L1-L4 lumbar arteries arise from the abdominal aorta severe atherosclerosis and

stenosis of these arteries and/or production of anti-calcific molecules by the injured vasculature may lead to more rapid regional bone loss and failure of the vertebral structure. These findings support previous prospective studies of older men and Chinese women that have reported the association between AAC and any vertebral fractures. (25,35,36)

Regarding incident fracture risk moderate to severe AAC was associated with increased clinical spine and clinical fractures, independent of age, treatment and BMD, while the association was attenuated for fracture-related hospitalizations and was non-significant for the few hip fractures that occurred. Importantly, while the absolute risk difference was relatively modest 5.4-7.6% over 10-years, this increased fracture risk was observed in 55% women (those with moderate to severe AAC) indicating that AAC may be an important fracture risk factor in older Caucasian women. Furthermore, AAC was associated with fracture independent of conventional fracture risk factors suggesting a novel potentially non-BMD mechanism. A previous nested case-cohort study in older women (n=951, mean age~ 72 years) found that an AAC24 score >4 assessed from DXA-derived lateral spine images was not associated with risk of non-vertebral fractures after 4 or 15-years, but was associated with higher 4-year risk of vertebral fractures and 5-year risk of hip fractures.(37) A prospective study of older men (n=5400, aged ≥65 years), found severe AAC was associated with a high risk of hip fracture but not non-hip fractures.(36) These discordant differences between the current study and the abovementioned studies may have been due to the cut-point selected, fracture ascertainment methods or population differences.

Another potential explanation is differences in the metabolic health of the cohorts, potentially modifying the relationship between AAC and incident fractures.

An interaction between AAC with HDLC for fracture outcomes was observed. Specifically, the relationship between AAC, clinical fractures and fracture hospitalizations was stronger in women with higher levels of HDLC that are typically associated with better metabolic health and reduced cardiovascular risk. HDLC is a recognised marker of reduced coronary heart disease and is anti-atherogenic via its anti-inflammatory and antioxidant properties.(38) These findings suggest that metabolic dysfunction associated with ageing may mask the true strength of the relationship between AAC and fractures. However, these findings should be interpreted with caution, as they are based on hypothesis generating analysis and need to be replicated in other cohorts of older women.

Women with both prevalent vertebral fractures and moderate to severe AAC had substantially higher incident fracture risk than either conditional alone. These findings suggest that concurrently capturing both prevalent vertebral fractures and AAC may identify a small (5.3%) but previously underappreciated high risk subset of women where fracture is remarkably common (10-year any fracture 45% and fracture hospitalization 24%).

There are a number of important limitations of our study that must be considered. Firstly, this was an observational study and as such causation cannot be established. Secondly, we cannot exclude the possibility of bias being introduced, particularly as the lateral spine images were only assessed in ~70% of the larger cohort. Furthermore, biomarkers were only available in a subgroup of women. Thirdly, the AAC24 point scale scoring system is only semi-quantitative and dependent on the reader's expertise. Nonetheless, a highly experienced investigator (J.T.S) read all images in this study. Fourthly, AAC was only assessed once at

baseline (between 1998 to 1999). Therefore, we cannot deduce the temporality of the association. Fifthly, we did not measure some established biomarkers of inflammation such as hs-CRP or TNF-alpha. Finally, as this cohort consisted predominantly of elderly Caucasian women with an average age of 75 years, these may not be generalizable to younger women, or men, or older women of other ethnicities.

Despite these limitations, the strengths of this study include the size of the cohort of older women that has similar disease burden and medication use to the population typically undergoing bone densitometry for osteoporosis screening. Additional strengths include, long-term prospective follow-up (10 years), capturing fracture events through both, verified self-report (by GP), as well as fracture-related hospitalizations and deaths from the Western Australian Data Linkage System independent of self-report. Furthermore, a single highly experienced investigator (J.T.S) assessed all lateral spine images in this study. Finally, we investigated the potential effect modifiers of the association capturing a range of disease processes such as metabolic dysfunction, renal function as well as circulating bone and vascular calcification biomarkers.

In conclusion, we have confirmed previous findings that increasing AAC is associated with increased prevalence of vertebral fractures, reduced hip BMD and have extended these findings to heel quantitative ultrasound measures. We also demonstrated robust associations between AAC and 10-year vertebral and non-vertebral clinical fractures, independent of clinical fracture risk factors. These findings add further support to the concept that vascular calcification and bone pathology may share similar mechanisms that remain to be fully elucidated. Finally women with both prevalent vertebral fractures and moderate to severe AAC had

substantially higher incident fracture risk than either conditional alone. These findings suggest that concurrently capturing prevalent vertebral fractures and AAC may identify a small but previously underappreciated group of women at high risk of future fracture.

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DISCLOSURES

K.E.W. is an employee of Hologic Inc. and reports personal fees, nonfinancial support, and other from Hologic, Inc., during the conduct of the study; personal fees and other from Hologic, Inc., outside the submitted work. In addition, K.E.W. has multiple densitometer imaging and reporting patents which may be relevant, United States and worldwide, both pending and issued, owned by Hologic, Inc. All other authors have no conflicts of interest to disclose.

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Table 1. Baseline characteristics and bone related variables stratified by abdominal aortic calcification (AAC) severity.

Demographics	All	Low AAC (AAC24 score 0 or 1)	Moderate AAC (AAC24 score 2-5)	Severe AAC (AAC24 score ≥6)
Number	1,024	459 (44.8)	373 (36.4)	192 (18.7)
Age, years	**75.0 ± 2.6**	**74.8 ± 2.6**	**74.9 ± 2.5**	**75.4 ± 2.7**
Heigth, cm	159.1 ± 5.7	159.2 ± 5.6	159.4 ± 5.9	158.0 ± 5.6
Weight, kg	68.5 ± 11.8	69.2 ± 12.3	69.4 ± 12.2	65.2 ± 9.3
More than 3 standard alcoholic drinks/day, yes (%)	35 (3.4)	14 (3.1)	13 (3.5)	8 (4.2)
Randomization				
Placebo, yes (%)	511 (49.9)	236 (46.2)	175 (34.2)	100 (19.6)
Calcium, yes (%)	485 (47.4)	212 (43.7)	186 (38.4)	87 (17.9)
Calcium plus vit D2, yes (%)	28 (2.7)	11 (39.3)	12 (42.9)	5 (17.9)
Smoker ever, yes (%)	**368 (35.9)**	**131 (28.5)**	**155 (41.6)**	**82 (42.7)**
Diabetes, yes (%)	57 (5.6)	22 (4.8)	24 (6.4)	11 (5.7)
Hip data				
Total hip area, cm	35.2 ± 3.2	35.3 ± 3.3	35.4 ± 3.1	34.8 ± 3.2
Total hip BMC, g	**28.7 ± 5.3**	**29.1 ± 5.5**	**28.7 ± 5.2**	**27.5 ± 5.2**
Total hip BMD, mg/cm^2	**0.81 ± 0.12**	**0.82 ± 0.13**	**0.81 ± 0.12**	**0.79 ± 0.12**
FRAX (Aust) with FN BMD	**8.0 ± 3.8**	**7.6 ± 3.4**	**8.0 ± 3.9**	**8.9 ± 4.0**

Heel (calcaneal) bone data				
Heel broadband ultrasound attenuation, db/Mhz*	**100.6 ± 7.9**	**101.2 ± 7.8**	**100.7 ± 7.9**	**99.1 ± 8.0**
Heel speed of sound, m/s*	1513 ± 25	1515.0 ± 25.7	1512.6 ± 24.7	1511.3 ± 25.1
Heel stiffness index, %*	**70.8 ± 11.3**	**71.6 ± 11.4**	**70.8 ± 11.1**	**69.1 ± 11.2**
Prevalent fracture from age 50 years				
Any fracture, yes (%)	**264 (25.8)**	**103 (22.4)**	**102 (27.3)**	**59 (30.7)**
Prevalent vertebral fracture from VFA				
None, yes (%)	**930 (90.9)**	**421 (91.7)**	**343 (92.2)**	**166 (86.5)**
One, yes (%)	**75 (7.3)**	**33 (7.2)**	**22 (5.9)**	**20 (10.4)**
Two or more, yes (%)	**18 (1.8)**	**5 (1.1)**	**7 (1.9)**	**6 (3.1)**
Grade of vertebral fractures				
None, yes (%)	**930 (90.9)**	**421 (91.7)**	**343 (92.2)**	**166 (86.5)**
Grade 1 only, yes (%)	**35 (3.4)**	**17 (3.7)**	**11 (3.0)**	**7 (3.6)**
Grade two or three, yes (%)	**58 (5.7)**	**21 (4.6)**	**18 (4.8)**	**19 (9.9)**
Location of vertebral fracture from VFA				
Thoracic VF, yes (%)	72 (7.0)	28 (6.1)	26 (7.0)	18 (9.4)
Lumbar VF, yes (%)[#]	**24 (2.3)**	**10 (2.2)**	**4 (1.1)**	**10 (5.2)**

Data expressed as mean ± SD or number and (%). AAC abdominal aortic calcification; BMD bone mineral density; BMC bone mineral content; FRAX Fracture risk assessment tool; VF vertebral fracture; Rows in bold represent significant differences (p-value<0.05) across AAC categories tested by ANOVA or Mantel-Haentzel test of trend where appropriate. *Measured in 990 participants at baseline. # Some patients had both thoracic and lumbar spine fractures.

Table 2. Hazard ratios (HR) for 10-year fracture risk by abdominal aortic calcification (AAC) category.

	Number of women with fracture (%)	**Age & treatment-adjusted HR (95%CI)**	**p value**	**Age, treatment & hip BMD - adjusted HR (95% CI)**	**p value**
Clinical fracture*					
Low AAC	94/459 (20.5)	**1 (reference)**		**1 (reference)**	
Moderate to severe AAC	159/565 (28.1)	**1.47 (1.14-1.90)**	**0.003**	**1.40 (1.08-1.81)**	**0.010**
Clinical vertebral fracture					
Low AAC	20/459 (4.4)	**1 (reference)**		**1 (reference)**	
Moderate to severe AAC	48/565 (8.5)	**1.98 (1.18-3.34)**	**0.010**	**1.84 (1.09-3.10)**	**0.023**
Clinical non-vertebral fracture					
Low AAC	80/459 (17.4)	**1 (reference)**		1 (reference)	
Moderate to severe AAC	130/565 (23.0)	**1.38 (1.04-1.82)**	**0.024**	1.32 (1.00-1.75)	0.051

Fracture hospitalization					
Low AAC	62/459 (13.5)	**1 (reference)**		1 (reference)	
Moderate to severe AAC	107/565 (18.9)	**1.42 (1.04-1.94)**	**0.028**	1.33 (0.98-1.83)	0.073
Hip fracture hospitalization					
Low AAC	22/459 (4.8)	1 (reference)		1 (reference)	
Moderate to severe AAC	39/565 (6.9)	1.43 (0.85-2.41)	0.186	1.31 (0.77-2.22)	0.315

AAC abdominal aortic calcification; BMD bone mineral density. *Clinical vertebral and non-vertebral fracture numbers do not equal total clinical fracture numbers as women may have suffered more than 1 fracture type. Rows in bold represent significant differences.

Table 3. Age and treatment-adjusted relative hazards for 10-year fracture in women with moderate-severe AAC vs. low AAC by potential clinical effect modifiers.

Subset according to baseline characteristic	**Clinical fracture (n = 263)**		**Fracture hospitalization (n = 169)**	
	HR (95%CI)	**p-value inter.**	**HR (95%CI)**	**p-value inter.**
Age (years)				
<75 years, (n=501)	**1.59 (1.08-2.33)**	0.858	1.40 (0.84-2.32)	0.815
≥75, (n=523)	1.39 (0.99-1.96)		1.46 (0.98-2.17)	

Smoking history				
No, (n=653)	1.37 (0.99-1.90)	0.724	**1.55 (1.04-2.33)**	0.338
Yes, (n=368)	1.50 (0.98-2.30)		1.20 (0.72-1.99)	
Treatment code				
Placebo, (n=511)	1.33 (0.94-1.86)		1.44 (0.92-2.27)	
Calcium, (n=485)	**1.77 (1.18-2.65)**	0.500	1.42 (0.90-2.23)	0.860
Calcium plus D2 (n=28)	0.47 (0.08-2.63)		0.89 (0.14-5.70)	
History of ASVD				
No, (n=912)	**1.43 (1.09-1.87)**	0.566	**1.45 (1.04-2.03)**	0.609
Yes, (n=112)	1.87 (0.80-4.34)		1.04 (0.42-2.55)	
eGFR, n=923				
≥60 ml/min/1.73m^2, (n=636)	1.37 (0.99-1.90)	0.897	1.71 (1.13-2.59)	0.124
<60 ml/min/1.73m^2, (n=287)	1.43 (0.87-2.32)		1.00 (0.57-1.76)	
Serum phosphate n=923				
Tertile 1, (n=294)	1.34 (0.81-2.22)		1.38 (0.76-2.50)	
Tertile 2, (n=303)	1.45 (0.90-2.34)	0.593	2.05 (1.08-3.88)	0.456
Tertile 3, (n=326)	1.40 (0.91-2.16)		1.11 (0.66-1.88)	
Serum calcium, n=923				

Tertile 1, (n=307)	1.61 (1.01-2.58)		1.54 (0.87-2.75)	
Tertile 2, (n=269)	1.32 (0.80-2.18)	0.433	1.14 (0.62-2.12)	0.982
Tertile 3, (n=347)	1.21 (0.77-1.89)		1.48 (0.85-2.58)	
History of diabetes				
No, (n=967)	**1.52 (1.17-1.99)**	0.211	**1.45 (1.04-2.02)**	0.434
Yes, (n=57)	0.84 (0.35-2.01)		1.02 (0.39-2.67)	
Systolic blood pressure				
<140 mmHg, (n=522)	**1.78 (1.26-2.52)**	0.120	1.54 (0.99-2.40)	0.948
≥140 mmHg, (n=473)	1.14 (0.77-1.70)		1.28 (0.80-2.03)	
Antihypertensive medications				
No, (n=589)	**1.41 (1.02-1.96)**	0.576	1.34 (0.89-2.00)	0.646
Yes, (n=435)	**1.67 (1.10-2.55)**		1.59 (0.95-2.65)	
Lipid lowering therapy				
No, (n=830)	**1.50 (1.13-1.99)**	0.754	**1.47 (1.04-2.09)**	0.465
Yes, (n=194)	1.38 (0.73-2.61)		1.11 (0.55-2.26)	
Body mass index				
<25 kg/m^2, (n=351)	**1.69 (1.10-2.59)**		1.37 (0.82-2.28)	
≥25-29 kg/m^2, (n=450)	1.28 (0.86-1.93)	0.266	1.28 (0.78-2.10)	0.753

≥30 kg/m^2, (n=223)	1.57 (0.92-2.66)		1.71 (0.86-3.38)	
HDLC, n=829				
<1.3 mmol, (n=293)	0.90 (0.54-1.48)	**0.071**	0.69 (0.36-1.32)	**0.007**
≥1.3 mmol, (n=536)	**1.55 (1.11-2.18)**		**2.00 (1.28-3.11)**	
Total cholesterol, n=829				
<5.3mmol, (n=610)	**1.41 (1.02-1.95)**	0.282	**1.62 (1.06-2.50)**	0.125
≥5.3 mmol, (n=219)	1.00 (0.59-1.71)		0.90 (0.48-1.72)	

AAC abdominal aortic calcification; ASVD atherosclerotic vascular disease. Hazard ratio (HR) for fracture compares the low vs. moderate to severe categories of AAC.

p-value inter. represents the p-value for the interaction ($p<0.1$) between severity of AAC (low vs. moderate to severe) with the listed variables as a continuous or binary variable where appropriate. Bolded values represent significant differences.

FIGURE LEGENDS

Figure 1. Kaplan Meier survival curves for 10-year a) clinical fractures and b) fractures requiring hospitalization by severity of AAC (black line=low AAC, dark grey line=moderate AAC and light grey line=severe AAC). Vertical lines represent censored cases.

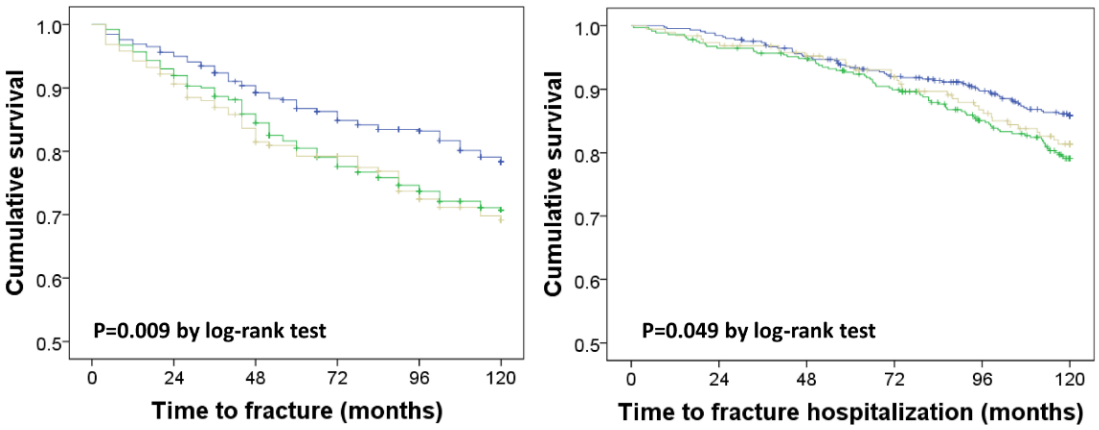

Figure 2. Multivariable-adjusted Cox proportional hazards regression for 10-year clinical fractures in (a) age and treatment-adjusted; (b) age, treatment and total hip BMD-adjusted models by moderate to severe AAC and presence or absence of prevalent vertebral fractures. Blue line = low AAC and no vertebral fracture [n=421], beige line = low AAC with vertebral fracture [n=38], green line = moderate to severe AAC and no vertebral fracture [n=510] and purple line = moderate to severe AAC with vertebral fracture [n=55].